The Tuberculosis Diagnostics and Treatment Pipeline for Children

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INTRODUCTION

An unacceptable disparity exists between the estimated burden of tuberculosis (TB) in children and the number actually diagnosed and put on TB treatment each year. In 2015, just 384,300 of an estimated one million children (38 percent) with TB were reported to national authorities.[1] To reach the remaining 62 percent of children with TB, efforts to identify children at risk for TB are urgently needed. Strategies should include household contact investigation programs, improved referral systems, and decentralized capacity to diagnose and treat childhood TB within maternal child health and primary care programs where sick children often first present for care. Research and development (R&D) will be critical to preventing, detecting, and curing TB in more children.

Enrollment in and planning of TB prevention, treatment shortening, and pharmacokinetic (PK) and safety studies in children continue to progress, in some cases producing interim results and bringing new pediatric formulations closer to market. Yet without intensified efforts to identify and screen children at risk of TB, the impact of these long-awaited advances will be severely limited. The inadequacy of existing diagnostic tests for children contributes to the challenge of finding and diagnosing children with TB.

This chapter discusses recent progress in R&D for pediatric TB diagnosis and treatment, highlights areas in need of further study, and makes recommendations to help expedite research necessary to further improve the diagnosis, prevention, and treatment of drug-susceptible (DS-) and drug-resistant (DR-) forms of TB in children.

DIAGNOSTICS

The World Health Organization (WHO) recommends several TB tests for use in children.[2,3,4] Existing tests and those under development that are designed to detect TB bacteria (see "The Tuberculosis Diagnostics Pipeline" beginning on page 91) are suboptimal for children, who often have fewer TB bacteria in their bodies than adults (paucibacillary disease). The usefulness of sputum-based tests is limited in young children, who often experience difficulty producing sputum and have high rates of extrapulmonary TB.[5] Even using the gold standard of culture, microbiological confirmation of TB is obtained in only 15–20 percent of children with clinically diagnosed TB.[6] Thus, most childhood TB is diagnosed empirically, based on presumption rather than confirmation of disease, using a combination of clinical and epidemiologic information. Given the limits of existing TB tests, empirical diagnoses are essential for children to access TB treatment. However, an empirical diagnosis offers no information about drug resistance—unless there is a close contact/index case with a defined resistance profile—and makes monitoring of treatment response difficult.

Efforts to optimize the performance of existing tests in children and to identify and validate gene signatures and biomarkers for use in the development of new tests for TB diagnosis and treatment monitoring are discussed below.

Optimizing Xpert for Children

The WHO's recommendations for the use of Xpert MTB/RIF (Cepheid, Sunnyvale, CA) in children apply to pulmonary and extrapulmonary specimens, including cerebrospinal fluid (CSF), lymph nodes, and other tissues.[7] A meta-analysis found that, while better than smear microscopy at detecting TB in samples from children, Xpert MTB/RIF is less sensitive than culture, which itself has imperfect sensitivity in children.

The sensitivity of Xpert MTB/RIF on induced or expectorated sputum from culture-negative children clinically diagnosed with TB was just two percent.[8] Research is ongoing to determine the sensitivity of Xpert MTB/RIF on alternative specimen types and to optimize specimen sample collection and processing to improve diagnostic yields in children.[9] Cepheid's second-generation Xpert cartridge, Xpert MTB/RIF Ultra (Ultra) appears to offer limited additional sensitivity.[10]

A prospective cohort study enrolling 272 HIV-positive children younger than 13 years old from eight hospitals in Burkina Faso, Cambodia, Cameroon, and Vietnam found that Xpert used on a combination of alternative samples (nasopharyngeal aspirate, stool sample, and string test) performed similarly to Xpert used on standard samples (gastric aspirate or expectorated sputum) in children with culture-confirmed TB (sensitivity: 75.9 vs. 72.4 percent).[11] Still, Xpert detected only 23 of 29 children (79.3 percent) with culture-confirmed TB and just 3 of 116 children (2.6 percent) with probable TB (classified using the Intrathoracic Tuberculosis Definitions for Diagnostic Research in Children[12]), maintaining the test's shortcomings and the diagnostic dilemma for children with culture-negative TB.[13]

A hospital-based study in 379 South African children younger than 13 years old found that the sensitivity and specificity of Xpert on stool were 31.9 percent and 99.7 percent, respectively, compared with bacteriologic confirmation by culture or Xpert on respiratory samples, including gastric or nasopharyngeal aspirates and induced or expectorated sputum. Just 45.1 percent of children with culture-confirmed TB and severe disease were stool Xpert positive. These findings suggest that the use of Xpert on stool may be limited to confirming TB in children who present with severe pulmonary TB disease. Compared with sputum or other samples, stool is less invasive and is relatively easy to collect from children, so Xpert on stool should be considered as a rule-in test with the potential to get sicker children started on TB treatment more quickly.[14]

Refinements made to increase the sensitivity of Xpert MTB/RIF by decreasing the clinical limit of detection 10-fold, from 130 to 10 colony-forming units per milliliter (CFU/mL), have resulted in the development of a second-generation cartridge, Ultra. In a multicenter study, Ultra demonstrated noninferiority to MTB/RIF. Ultra was 17 percent more sensitive than MTB/RIF among participants with smear-negative, culture-positive TB (see "The Tuberculosis Diagnostics Pipeline," page 91). In pediatric studies, Ultra demonstrated sensitivity of 95 percent compared with 45 percent for MTB/RIF for the detection of TB meningitis (TBM) in CSF and 71 percent sensitivity versus 47 percent for MTB/RIF on pediatric respiratory samples.[15] Ultra's higher sensitivity over MTB/RIF on pediatric pulmonary and extrapulmonary TB samples is an important advance but, again, may not confer much benefit to children with culture-negative TB.

The Unitaid-funded TB SPEED (**S**trengthening **P**ediatric TB Services for **E**nhanced **E**arly **D**etection) project is one of two grants awarded under Unitaid's 2016 call for proposals to scale up better TB treatment for children.[16] The project, to be implemented by the University of Bordeaux in Sierra Leone, Côte D'Ivoire, Cameroon, Uganda, Mozambique, and Uganda, includes operational research to test an innovative decentralized diagnostic strategy and to optimize the collection and processing of alternative pediatric samples, including stool and nasopharyngeal aspirates. The project also includes a randomized clinical trial to improve TB detection among children with severe pneumonia (*N* = 3,000 children <5 years old). Market impact and forecasting analyses will build an evidence base for future scale-up of effective interventions identified by the TB SPEED project.[17]

Optimizing the performance of existing tests in populations known to produce smear- and culture-negative samples (e.g., children, people living with HIV) remains important. Several efforts are under way, but to radically improve rates of confirmed TB diagnosis in children with TB, a next-generation, rapid diagnostic test that is not sputum or pathogen based, and instead dependent on the host's immune response, may be required.

Developing New Tests for Children

Numerous reports have emerged on candidate gene signatures and biomarkers capable of differentiating between TB disease states in pediatric and adult cohorts. Yet few have been independently validated and translated into diagnostic tests relevant to clinical practice.[18] A systematic review of biomarker studies found that of 399 candidate biomarkers of TB disease, just 12 have been confirmed in prospective studies, and only one—lipoarabinomannan (LAM)—has been translated into a clinical assay and endorsed by the WHO (Alere Determine LAM).[19] Several factors limit the advancement of gene signatures and biomarkers from discovery to further stages of development, chief among them the size and cost of independent validation studies given the limited funding for TB R&D, in particular TB diagnostics research.[20]

The following sections provide updates on promising gene signatures and biomarker-based assays in development for the diagnosis of children with TB, as well as recommendations to further advance research and development in this area.

Gene Signatures

A gene signature is a group of genes differentially expressed under certain biological or other conditions, for example, in the presence of TB infection or disease. In 2014, Anderson et al. from the ILULU Consortium published the performance of a 51-transcript signature for distinguishing TB disease from other diseases and from TB infection in children.[21] Since these findings were published, to facilitate translation into a point-of-care diagnostic, the ILULU Consortium has narrowed its signature down from 51 to three genes. For distinguishing TB from other diseases, the three-gene signature demonstrated 93.3 percent sensitivity and 80 percent specificity in pediatric test data sets from South Africa and Malawi and 95.5 percent sensitivity and 73.1 percent specificity in a pediatric validation data set from Kenya. Work to refine the selected thresholds to further improve the specificity of the three-gene signature is ongoing.[22]

Sweeney et al. from the Stanford Institute for Immunity, Transplantation and Infection identified a different but overlapping three-gene signature, which they validated in 11 independent data sets including both children and adults from 10 countries. Their three-gene signature demonstrated 86 percent sensitivity and specificity for TB infection versus culture-positive TB in children, but TB scores in children with culture-negative TB were significantly lower than those in children with culture-positive TB, suggesting lower sensitivity in children with culture-negative TB.[23] Since these findings were published in 2016, the Stanford Institute for Immunity, Transplantation and Infection has conducted a prospective validation study of its three-gene signature in a cohort from Brazil. Further information regarding study design was not available at the time of writing, but published results are expected soon.[24]

Biomarker-Based Assays

C-Tb for TB infection

The Statens Serum Institute's C-Tb test is a skin test based on ESAT-6 and CFP10, antigens specific to TB that are also the foundation of interferon gamma release assays (IGRAs). Like the tuberculin skin test (TST), the C-Tb test does not require a laboratory. It has improved specificity that, in contrast to the TST, is not affected by BCG vaccination. A phase III trial, including 86 participants 5–17 years old and 35 younger than 5 years old from Spain, found the C-Tb test safe and highly concordant with IGRAs in individuals aged 5 years and older. Positive results increased with the risk of TB infection.[25] These findings should be interpreted with caution, as the trial was not powered to test C-Tb's performance in the pediatric subgroup. A separate phase III trial conducted in South Africa, including 600 children, found

that C-Tb, TST, and IGRAs performed equally well, but low CD4+ T cell counts (<100 cells/mm3) reduced test performance.[26,27] More complete published results are expected soon.[28]

TAM-TB for TB disease

The TAM-TB test is a rapid, blood-based T-cell activation marker assay that has so far been evaluated in adults and a small cohort of HIV-positive and HIV-negative Tanzanian children six months to 16 years old (*N* = 113). In this prospective proof-of-concept study, the TAM-TB assay demonstrated 83.3 percent sensitivity among children with culture-confirmed TB and 96.8 percent specificity among children classified as not having TB. Sensitivity was highest in culture-positive cases and decreased with decreasing clinical diagnostic certainty (38 percent in children with highly probable TB; 17 percent in children with probable TB).[29] Further assessments of TAM-TB's performance, especially in young, malnourished, and HIV-positive children, are needed. After a long period without funding, this assay is now being developed into a kit version. A small study to evaluate the kit version of the TAM-TB assay, funded by the German Center for Infection Research (DZIF), is expected to open to enrollment in Munich in 2017. Further funding to evaluate the TAM-TB test in adults and children from high TB burden settings is currently being sought.[30]

Recommendations

Despite continued incremental progress in improving the sensitivity of existing TB tests and diagnostic strategies in children, a point-of-care test that can accurately detect TB in children, especially those with culture-negative disease, remains elusive. Radically improving rates of diagnosis in children with TB will require a gene signature or biomarker-based test that is not sputum based.

Studies to discover new candidate gene signatures and biomarkers are numerous, but those to test and validate them against clinical endpoints in heterogeneous populations are rare. Efforts are needed to reduce gaps between discovery, validation, and translation into diagnostic tests that will benefit children with TB. Toward this end, increased investments in research to discover and validate gene signatures and biomarkers, and innovation to translate these into simple and affordable tests for TB, are necessary. In 2015, just $4.4 million and $2.2 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively.[31]

Evaluating promising biomarkers and gene signatures identified in adult cohorts in children is important, but pediatric-specific discovery and validation efforts remain necessary, especially considering age-dependent differences in the immune response to TB and the broad spectrum of TB disease observed in children.[32] Basic scientists and clinical investigators should seek out and foster collaborations in order to maximize knowledge gained by promoting the implementation of substudies within ongoing or planned pediatric studies, including treatment trials, to help identify or validate gene signatures or biomarkers of TB that are reliable independent of age, nutritional status, and coinfection with other pathogens common in children with TB (HIV, pneumonia, etc.) and sensitive enough to detect culture-negative or paucibacillary TB.

Harmonized and collaborative biorepositories are critical to biomarker discovery and development. The Foundation for Innovative New Diagnostics is developing a curated TB biomarker database linked to its biobank, allowing for streamlined validation of biomarkers using well-characterized specimens from diverse patient populations across a variety of ages and geographic regions.[33] Researchers should consider contributing their data sets to this and other publically accessible databases such as the U.S. National Institutes of Health Gene Expression Omnibus.

In the meantime, there is an urgent need to scale up and decentralize screening and diagnosis of pediatric TB infection and disease using a combination of existing tools and empirical diagnoses. Globally, despite significant scientific advances, death rates for childhood TB have not changed between the pretreatment era (before 1946) and 2016 (21.9 vs. 22 percent).[34,35] This dismal finding highlights the large proportion of children with TB who are not detected and, as a result, die untreated each year. This seems particularly egregious given the extent of pediatric TB treatment R&D efforts discussed in the next section.

TREATMENT

TB prevention, treatment shortening, and PK and safety studies in children continue to progress, in some cases producing interim results and bringing new pediatric formulations closer to market. Table 1 provides an overview of ongoing and planned pediatric TB prevention and treatment studies. The subsequent section offers updates on studies that have advanced or produced results within the last year.

Table 1. Ongoing and Planned TB Prevention and Treatment Studies in Children

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
Titi 3 months of isoniazid and rifampin or 6 months of isoniazid for prevention of TB (implementation study)	Enrolling; final results expected 2018	HIV-positive and HIV-negative infant and child contacts <5 years old	Expertise-France/the Union
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–12 years old with LTBI	TBTC, Sanofi
TB-CHAMP 6 months of levofloxacin vs. placebo for prevention of MDR-TB (substudy planned using delamanid for child contacts of FQ-R TB patients)	Planned; opening 2017	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/ IMPAACT P2003 (PHOENIx) 6 months of delamanid vs. isoniazid for prevention of MDR-TB	Planned; opening 2018	High-risk (HIV+, TST+, or <5 years old) infant, child, adolescent, and adult household contacts of index patient with MDR-TB	NIAID, NICHD
V-QUIN 6 months of levofloxacin vs. placebo for prevention of MDR-TB	Enrolling; final results expected 2020	HIV-positive or HIV-negative adult household contacts; inclusion of adolescents and children <15 years old expected in 2017	NHMRC
TREATMENT – DRUG-SENSITIVE TB			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results published 2016	HIV-positive or HIV-negative infants <12 months old with TB	Unitaid/TB Alliance (STEP-TB Project)

Study/Regimen	Status	Population(s)	Sponsor(s)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrollment complete; results presented 2016	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
OptiRif Kids PK, safety, and dose optimization of rifampin for treatment of TB	Enrolling; results expected 2019	HIV-negative infants and children 0–12 years old with TB	TB Alliance
SHINE 4 vs. 6 months using 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of nonsevere TB	Enrolling; results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with nonsevere TB	BMRC, DFID, Wellcome Trust
TBM-KIDS Safety and efficacy of high-dose rifampin ± levofloxacin for treatment of TBM	Enrolling; results expected 2019	HIV-positive or HIV-negative infants and children with TBM	NICHD
COTREATMENT WITH ARVs			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; results expected 2018	HIV-positive or HIV-negative low-birth-weight/premature infants	NIAID, NICHD
PK-TBHIV02 PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrollment complete; results presented 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, NICHD
PK-PTBHIV03 PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
HIVPED001 PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; results presented 2016	HIV-positive infants and children with TB weighing 3–15 kg; DNDi developing standalone ritonavir booster formulation	DNDi, AFD, UBS Optimus Foundation, MSF
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2018	ARV-naive, HIV-positive children and adolescents 2–12 years old with TB	NIAID, NICHD

Study/Regimen	Status	Population(s)	Sponsor(s)
ODYSSEY PK and safety of dolutegravir with rifampin-containing TB treatment NCT02259127*	Enrolling; results expected 2019	HIV-positive children and adolescents 6–12 years old with TB	PENTA Foundation
IMPAACT P2006 Dolutegravir vs. lopinavir/ritonavir and interactions with rifampin-containing TB treatment	Planned	HIV-positive infants and children 1 month to 3 years old with TB	NIAID, NICHD
TREATMENT – DRUG-RESISTANT TB			
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrollment complete; interim results presented; final results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Enrolling; interim results presented; final results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; final results expected 2018	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; final results expected 2020	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT P2005 PK and safety of delamanid; all-oral OBR for treatment of MDR-TB	Planned; opening 2018	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, NICHD
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Enrolling; final results expected 2025	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, NICHD
*U.S. National Institutes of Health clinical trial identifiers; for more information, go to ClinicalTrials.gov.			

AFD: French Development Agency
ART: antiretroviral therapy
ARV: antiretroviral
BMRC: British Medical Research Council
CIHR: Canadian Institutes of Health Research
DFID: Department for International Development (United Kingdom)
DNDi: Drugs for Neglected Diseases Initiative
FDC: fixed-dose combination
FLD: first-line drug
FQ-R: fluoroquinolone-resistant
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
LTBI: latent tuberculosis infection
MDR-TB: multidrug-resistant tuberculosis
MSF: Médecins Sans Frontières
NHMRC: National Health and Medical Research Council (Australia)
NIAID: National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health
OBR: optimized background regimen
PENTA: Pediatric European Network for Treatment of AIDS
PK: pharmacokinetics
SA MRC: South African Medical Research Council
SLD: second-line drug
TB: tuberculosis
TBM: tuberculous meningitis
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
TST: tuberculin skin test
UBS: Union Bank of Switzerland
WHO: World Health Organization

Research Updates

TB Prevention Studies

The Union's **Titi** study of three months of daily isoniazid and rifampin (3HR) or six months of daily isoniazid (6H) to prevent TB disease in children under five years old opened to enrollment in 2016. This study will evaluate the feasibility of implementing these two regimens in infant and child contacts of people with DS-TB. Children treated with 3HR will receive the new pediatric fixed-dose combination (FDC) of isoniazid and rifampin developed for use during the continuation phase of active TB treatment. Results are expected at the end of 2018.[36]

Tuberculosis Trials Consoritium study 35 (**TBTC** S35) is poised to open for enrollment in 2017. This study follows Sanofi's completion of a bioavailability and safety study of the components of its fixed-dose dispersible of rifapentine and isoniazid (HP) and a rifapentine (P) stand-alone dispersible to be used to facilitate dose adjustments in young children.[37] These formulations will be used in TBTC S35 to evaluate the PK and safety of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB disease in children. Discussions regarding the investigational new drug status of the study and initial challenges in formulation development have contributed to a series of delays in the study's progress.

TB CHAMP, which will evaluate whether six months of levofloxacin can prevent multidrug-resistant (MDR-TB) disease in household contacts under five years old, is poised to open for enrollment this year. Macleods completed a small bioavailability study of its dispersible formulation in adults. A lead-in PK substudy to test levofloxacin exposures achieved in children with the new dispersible formulation is underway. The trial is expected to open at three sites in South Africa in the second half of 2017.[38]

V-QUIN, designed to evaluate whether six months of levofloxacin can prevent MDR-TB disease in adult household contacts, is currently enrolling children for periodic screening for disease, without randomization. The investigators expect to commence randomization of adolescents and children <15 years old in the second half of 2017, pending an upcoming resubmission to the National Ministry of Health Ethics Committee in Viet Nam.[39]

The AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) networks successfully completed a feasibility study in advance of the **PHOENIx** trial, which will compare six months of delamanid to isoniazid to prevent MDR-TB disease in household contacts of people with confirmed MDR-TB and is expected to open in early 2018.[40]

TB Treatment Studies

DS-TB

A study of first-line treatment in infants and children in Ghana (**PK-PTBHIV01**; *N* = 113; 47.8 percent of children less than five years old), using WHO-recommended doses, found that children with HIV and TB had significantly lower exposures to rifampin, pyrazinamide, and ethambutol than children with TB alone.[41] This is one of several studies that have found that the higher doses recommended for children by the WHO starting in 2010 still produce lower drug exposures measured by Cmax (peak drug exposure) and area under the curve (AUC, or total drug exposure) in children compared with adults.[42]

Given the previously demonstrated association between low drug exposures and poor treatment outcomes in children,[43] there is an urgent need to determine whether exposures with recommended doses for children result in good outcomes, even if they do not match the levels achieved in adults.

The **SHINE** study, which opened to enrollment in the third quarter of 2016, will evaluate whether it is possible to shorten treatment from six to four months for less-severe smear-negative forms of TB in children. The SHINE study uses the new pediatric FDCs aligned with WHO-recommended doses and includes nested PK studies in both HIV-positive and HIV-negative participants. Since SHINE is powered to look at efficacy, it may be able to provide some insights as to whether currently recommended doses for first-line TB drugs in children and the exposures they achieve are adequate (achieve good outcomes). These insights may be limited in their applicability to children with more severe forms of TB (i.e., miliary TB, TBM, and other extrapulmonary manifestations) that likely require higher levels of drug exposure in order for drugs to reach each of the infected sites and to exert their effects.

OptiRif Kids, which opened in the first quarter of 2017, will further explore low rifampin exposures observed in other studies in young children[44] and evaluate rifampin doses necessary to achieve exposures in children that match higher doses evaluated in adults (up to 35–40 mg/kg) and found to be safe, well tolerated, and able to kill more mycobacteria (see "The Tuberculosis Treatment Pipeline," beginning on page 129). Starting with the currently WHO-recommended dose, modeling techniques will be used to determine escalating doses to be evaluated in the study cohorts.

Modeling has also informed the higher dose of rifampin (recommended range: 10–20 mg/kg) that will be administered to some of the children with TBM enrolled in **TBM-KIDS**.[45] Children will be randomized to receive the standard of care (isoniazid, rifampin, pyrazinamide, and ethambutol); isoniazid, pyrazinamide, ethambutol, and high-dose rifampin (30 mg/kg); or isoniazid, pyrazinamide, high-dose rifampin (30 mg/kg), and levofloxacin dosed at 20 mg/kg for children older than two years and 15 mg/kg for children two years old or younger (recommended range: 10–15 mg/kg once daily for children older than five years of age and 15–20 mg/kg split into two doses for children five years of age or younger). The investigators expect the 30 mg/kg dose of rifampin to achieve exposures in children that approximate those from recent studies to optimize the treatment of TBM in adults. Neurologic and neurocognitive outcomes will also be assessed and PK/PD relationships explored.[46]

Cotreatment With Antiretrovirals

HIVPED001, a study evaluating superboosted lopinavir/ritonavir administered in a ratio of 1:1 (standard lopinavir/ritonavir is administered in a ratio of 4:1) with rifampin-containing TB treatment to infants and young children, produced final results in 2016. The study determined that exposures following superboosted doses of lopinavir/ritonavir (1:1) with rifampin are noninferior to exposures following standard doses of lopinavir/ritonavir (4:1) without rifampin.[47] Virological efficacy and safety were also comparable. These results led to strengthened WHO recommendations to use superboosting in TB/HIV co-infected children on lopinavir/ritonavir.[48] Acceptability of existing standalone liquid formulations of ritonavir is poor on account of their taste. The Drugs for Neglected Diseases Initiative and Cipla developed and tested several taste-masked granule and pellet formulations of ritonavir, but they were unable to cover the bitter taste without compromising bioavailability. The Drugs for Neglected Diseases Initiative plans to test the acceptability of a powder formulation developed by AbbVie that is bioequivalent to the existing liquid formulation but not taste masked.[49]

Studies to characterize drug-drug interactions (DDIs) between rifampin and anti-HIV compounds, including integrase inhibitors (**P1101; ODYSSEY; P2006**), in children are ongoing. The availability of alternative HIV regimens for children with TB has gained attention as rates of resistance to non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine) have increased among children.[50] DDIs between rifampin and protease inhibitors (e.g., lopinavir and ritonavir), though possible to overcome as discussed above, make dosing difficult.

DR-TB

Estimates of the burden of MDR-TB among children range from 25,000 to 32,000 cases per year.[51,52] Yet few children globally are treated for MDR-TB. An individual patient systematic review and meta-analysis of children treated at any time in the past for MDR-TB identified only 1,000 such children.[53] Severe gaps in diagnosis and difficulties obtaining bacteriologic confirmation in children might explain this vast discrepancy, but the historical lack of experience with, knowledge about, and child-friendly formulations of the second-line TB drugs used to treat MDR-TB likely contribute, as well.

Encouragingly, there has been increased activity in this area in recent years. Studies designed to fill PK and safety data gaps to inform the safe and optimal use of existing and new second-line drugs in children have produced interim results, and studies to shorten and improve treatment regimens have included limited numbers of adolescents and children or are in advanced stages of planning for these populations.

PK and Safety Data

Ongoing analyses of data collected in **MDR-PK 1**, which completed enrollment in 2015, and **MDR-PK 2**, still open, continue to produce pediatric PK and safety information for existing second-line drugs, including levofloxacin, moxifloxacin, linezolid, ethionamide, para-aminosalicylic acid, terizidone, and other drugs. Pediatric studies of the newer second-line drugs delamanid, bedaquiline, and pretomanid continue to progress, but at very different paces.

Population PK models, combining PK data from multiple individuals, can predict and simulate how drugs behave in the body. A population PK model built using data from 109 children treated with levofloxacin in MDR-PK 1 determined that levofloxacin dosed at 20 mg/kg (recommended range: 10–15 mg/kg once daily for children more than five years of age; 15–20 mg/kg split into two doses for children five years of age or younger) achieved lower levels of exposure in children than in adults.[54] The model predicted that the 30–40 mg/kg doses required for children to achieve exposures matching those in adults would produce higher peak exposures, raising safety concerns. In MDR-PK 1, levofloxacin dosed at 15–20 mg/kg was safe and well tolerated.[55]

A population PK model of moxifloxacin in children with and without HIV, built using data from 52 children in MDR-PK 1 and MDR-PK 2, determined that at currently recommended doses (range: 7.5–10 mg/kg) children achieve considerably lower moxifloxacin exposures than adults.[56] Higher moxifloxacin doses need to be explored and evaluated for safety in children.

A population PK model of linezolid in children with and without HIV, built using data from 17 children enrolled in MDR-PK 1 and MDR-PK 2, determined that at currently recommended doses (range: 10 mg/kg three times a day) children achieve linezolid exposures that approximate those achieved in adults, and that twice-daily dosing in young children may result in exposures that exceed those achieved in adults.[57] These data highlight the importance of ongoing PK and safety investigations of second-line and new TB drugs in children, especially given the potential for dose-dependent toxicities.

Data collected from participants in MDR-PK 1 treated with moxifloxacin and linezolid will be rolled into MDR-PK 2, which remains open to enrollment and will further examine the PK and safety of optimized doses of moxifloxacin, levofloxacin, and linezolid in children.[58] Simulations with these models and data will determine optimal weight-banded dosing schemes for these drugs in children. Optimal dosing strategies for clofazimine in children may also be evaluated in this project.

Data from **C232/C233** (a pediatric PK and safety study of delamanid in HIV-negative children) have informed a decision by the WHO to extend its recommendations on the use of delamanid for

the treatment of MDR-TB in adults to children six years and older and adolescents, using the adult formulation.[59] Studies with the pediatric formulation are underway: follow-up for the three- to five-year-old cohort is ongoing, and the fourth and final age cohort (children younger than 2 years old has started enrollment.[60] IMPAACT **P2005** will provide complementary delamanid PK and safety data in children with MDR-TB, including those with HIV infection, in the context of all-oral regimens.[61]

In December 2012, the U.S. Food and Drug Administration (FDA) granted accelerated approval for bedaquiline in adults, but pediatric investigations of bedaquiline only began in March 2016. As a result, limited data are available and the WHO has not been able to make a recommendation about the use of bedaquiline in adolescents or children.[62] However, bedaquiline is already being used to treat adolescents and children down to 12 years old in some programs under certain conditions.[63] At the time of writing, Janssen's pediatric PK and safety study of bedaquiline (**C211**) was enrolling at sites in South Africa, Russia, and the Philippines and had recruited just 15 participants to the first and second age cohorts (7- to 18-year-olds).[64] Results from the first two cohorts will be available in 2018. The site Janssen opened in Russia has so far been able to enroll only adolescents. Discussions between Janssen and the Russian regulatory authorities on the possibility of enrolling younger children are ongoing. Janssen expects a site in India to open to enrollment at the end of this year, which may help to speed up recruitment.[65] **P1108**, the IMPAACT network's pediatric PK and safety study of bedaquiline, including in HIV-positive children, is expected to open by mid-2017. P1108 uses model-based dosing strategies and modified age de-escalation; data will be disseminated as each cohort is enrolled.

The pretomanid-containing NiX-TB regimen has produced promising preliminary results (see TB Treatment Pipeline, in *2017 Pipeline Report*, [publishing July 2017]), and the TB Alliance is currently advancing plans for a phase III trial. FDA concern regarding testicular toxicity observed in rodents in preclinical studies stalled the initiation of pediatric investigations of pretomanid.[66] The TB Alliance has submitted male reproductive hormones data collected from participants in its phase II and III studies of pretomanid to the FDA to alleviate its concern and gain agreement that children may be dosed with pretomanid. It plans to submit a Pediatric Investigational Plan (PIP) to the European Medicines Agency (EMA) in mid-2017 and has already developed a dispersible formulation.[67]

Shortened Regimens

In May 2016, the WHO issued an update to its guidelines for treating MDR-TB, recommending the use of a shortened regimen (nine months of moxifloxacin, clofazimine, ethambutol, and pyrazinamide, given with kanamycin, prothionamide, and isoniazid for the first four months) in children with confirmed rifampin-resistant or MDR-TB.[68] This recommendation was based on data collected in adults, but operational research conducted by the Union in collaboration with national TB programs in nine African countries has provided some data on the performance of, and practical experience implementing, the shortened regimen in adolescents and children.

Using the shortened regimen, the Union reported a treatment success rate of 83 percent among 47 children and adolescents (19 percent HIV-positive).[69] These findings should be interpreted with caution given the small sample size and that just five of the children enrolled were under 10 years old. While adverse events were reportedly "mild," high rates of observed gastrointestinal toxicity (74 percent) and ototoxicity (41 percent) underscore the urgent need for similarly short regimens, made up of less-toxic and better-tolerated drugs.

The paucibacillary nature of TB disease in children, and the improved MDR-TB treatment outcomes observed among children compared to adults,[70] even with observed lower exposures to key second-line drugs, suggest that it might be possible to treat MDR- TB in children using shorter and less aggressive regimens than those necessary in adults.[71] The shortened regimen could be a major improvement but still requires a lot of drugs, including an injectable agent, with unacceptable toxicity. Studies to determine whether it is possible to treat MDR-TB in children using all-oral regimens that contain fewer drugs are urgently needed.

SMaRT Kids, a randomized phase III trial for which a protocol is currently under development (currently unfunded), proposes to test an all-oral, six-month regimen of delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide against the WHO-recommended shortened regimen in children younger than 13 years old with rifampin-resistant or MDR-TB. The study will evaluate six months of delamanid, clofazimine, linezolid, para-aminosalicylic acid, and pyrazinamide against 18- to 24-month individualized regimens built according to WHO recommendations in children with pre-extensively drug-resistant and extensively drug-resistant TB.[72]

The wide spectrum of TB disease presentation in children, ranging from severe disease (e.g., miliary disease or TBM) in young children to limited pulmonary disease to cavitary disease in adolescents, makes selecting a regimen and duration of treatment appropriate for all children and adolescents difficult. A one-size-fits-all approach is likely to result in under- or overtreatment in certain groups of children with TB.[73] Discussions of the optimal design, regimen, and population for inclusion in SMaRT Kids continue.[74]

Formulation Updates

Under the Unitaid-funded Step-TB project, implemented by the TB Alliance, appropriately dosed pediatric FDCs of first-line TB drugs were finally introduced to the market at the end of 2015. Uptake has been slow due to logistical and other challenges at the country level, but recent efforts by key organizations through their participation in the Stop TB Partnership Global Drug Facility–convened TB Procurement Market Shaping Action Team (TPMAT) have helped country programs develop and expedite plans to facilitate transition to the new formulations. A second quality-assured source necessary to ensuring market stability and competition, though anticipated, has yet to reach the market.

In contrast to first-line TB drugs, just five of 14 second-line TB drugs are available in pediatric formulations, and even these are inadequate. Existing oral suspensions (syrups) of linezolid and levofloxacin are difficult to dose accurately, are bulky and difficult to ship and store, and are not widely available.[75] Moxifloxacin (only available in a 400 mg tablet), which is not scored and bitter when crushed, and clofazimine (only available in soft gel capsule form) are core components of MDR-TB treatment, including the WHO-recommended shortened regimen, but are hard to give in appropriate doses to children with existing adult formulations. Pediatric formulations of moxifloxacin, clofazimine, and other key second-line TB drugs are an urgent priority.

Encouragingly, Macleods has been working to develop dispersible levofloxacin, moxifloxacin, linezolid, and ethionamide and a minicapsule of cycloserine. Macleods' scored dispersible 100 mg levofloxacin formulation, currently undergoing PK and acceptability testing in children, will be piloted in the TB-CHAMP trial. With support from the U.S. National Institute of Allergy and Infectious Diseases Small Business Initiative for Research Program, Luna Innovations has been working to create pediatric gummy formulations of ethambutol, isoniazid, moxifloxacin, and clofazimine. They have created gummies in FDCs of isoniazid, rifampin, and pyrazinamide (HRZ) and isoniazid and rifampin (HR). Luna Innovations is currently working with the IMPAACT network to perform stability testing and hopes to initiate animal studies in 2018.[76] Pediatric formulations in development or new to the market are summarized in Table 2.

Table 2. Pediatric Formulations in Development or New to Market

Drug	Dose	Formulation	Company	Status
First-line drugs				
Fixed-dose combinations	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Macleods	Passed GF ERP; in distribution; PQ dossier under assessment*
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Lupin	Status unknown
	HRZ: 50/75/150 mg HR: 50/75 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Sandoz	Status unknown
	HRZ: 50/75/150 mg HR: 50/75 mg HP: 150/150 mg	Dispersible tablet	Sanofi	HRZ/HR: Status unknown HP: Product developed; soon to be in clinical trial
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Svizera	Status unknown
Ethambutol	100 mg	Dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Isoniazid	100 mg	Dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Pyrazinamide	150 mg	Dispersible tablet	Macleods	PQ granted; distribution status unknown
Rifapentine	100 mg	Dispersible tablet	Sanofi	Product developed; soon to be in clinical trial
Second-line and new drugs				
Bedaquiline	20 mg	Dispersible tablet	Janssen	Product developed; soon to be in clinical trial
Clofazimine	10 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Cycloserine	125 mg	Mini capsule	Macleods	Passed GF ERP; distribution status unknown
Delamanid	20 mg 5 mg	Dispersible tablet	Otsuka	Undergoing clinical trial
Ethionamide	125 mg	Scored dispersible tablet	Macleods	PQ granted; distribution status unknown
	125 mg	Scored dispersible tablet	Lupin	Status unknown
Levofloxacin	100 mg	Scored dispersible tablet	Macleods	Passed GF ERP; distribution status unknown
Linezolid	150 mg	Dispersible tablet	Macleods	Status unknown
Moxifloxacin	100 mg	Scored dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Pretomanid	50 mg 10 mg	Dispersible tablet	TB Alliance	Product developed; soon to be in clinical trial

*The status of this formulation is speculative and based on available information, as the WHO does not provide information linking PQ dossiers under assessment to manufacturers. The manufacturer was contacted to confirm the status listed here but did not respond.

GF ERP: Global Fund Expert Review Panel
H: isoniazid
P: rifapentine
R: rifampin
PQ: Prequalification
Z: pyrazinamide

Box 1. TB Research Updates for Pregnant Women

Despite substantial clinical need for TB prevention and treatment, pregnant women remain neglected by research initiatives. In recent years, pregnant women have started to see modest representation in TB clinical trials.

Table 3. Ongoing and Planned TB Prevention and Treatment Studies in Pregnant Women

Trial	Phase	TB type	Study purpose
PREVENTION			
IMPAACT P1078 (TB APPRISE) NCT01494038*	IV	DS-TBI	To evaluate antepartum vs. postpartum isoniazid preventive therapy in HIV-positive women
IMPAACT P2001 NCT02651259*	I/II	DS-TBI	To evaluate the pharmacokinetics and safety of once-weekly rifapentine and isoniazid in pregnant and postpartum women with and without HIV
TREATMENT			
IMPAACT P1026s NCT00042289*	IV	DS-/DR-TB	To evaluate the pharmacokinetics of first- and second-line TB drugs with and without ARVs in pregnant women
ACTG A5338 NCT02412436*	IV	DS-TB	To evaluate the pharmacokinetic interactions among depo-medroxyprogesterone acetate, rifampin, and efavirenz in women co-infected with HIV and TB
THSEPISO	IV	DS-TB	To study the impact of TB/HIV coinfection in pregnancy on maternal and infant outcomes and to evaluate the pharmacokinetics of first-line TB drugs in pregnant and postpartum women
TB pregnancy registry	IV	DS-/DR-TB	To evaluate maternal and infant treatment and safety outcomes from clinical research databases (planned)
*U.S. National Institutes of Health clinical trial identifiers; for more information, go to ClinicalTrials.gov.			

ARV: antiretroviral
DR-TB: drug-resistant tuberculosis
DS-TB: drug-sensitive tuberculosis
DS-TBI: drug-sensitive tuberculosis infection
TB: tuberculosis

An evaluation of 87 women who became pregnant while participating in two studies comparing three months of weekly rifapentine (900 mg) and isoniazid (900 mg) to nine months of daily isoniazid (300 mg) found that the combination regimen (3HP) was not associated with adverse pregnancy outcomes.[77] Further safety and PK investigations of 3HP are necessary in pregnant and postpartum women and are planned in IMPAACT **P2001**, which opened to accrual in the first quarter of 2017. Investigators should attempt to collect safety and other data in women who become pregnant while participating in TB research studies to help inform the prevention and treatment of TB in pregnant and postpartum women in the time between when interventions are formally tested in nonpregnant versus pregnant populations.

IMPAACT **P1078**, a phase IV study to evaluate the safety and toxicity of isoniazid preventive therapy (IPT) administered during pregnancy (second or early third trimester) or three months postpartum, has enrolled 950 mother-infant pairs from eight countries. Primary results are expected by the end of 2017. The study will provide information about the safety and optimal timing of IPT in pregnancy, PK and interactions between isoniazid and antiretroviral therapy, and TB-specific immune responses in pregnancy and postpartum.[78]

Samples from 34 pregnant and postpartum women enrolled in the **TSHEPISO** study, previously analyzed to characterize PK and DDIs for rifampin, isoniazid, and efavirenz,[79,80] are now undergoing further analyses and are expected to produce additional information regarding the PK of ethambutol and pyrazinamide.[81] A publication describing the impact of TB/HIV coinfection in pregnancy on maternal and infant outcomes is expected in 2017.[82]

P1026s, the IMPAACT network study to evaluate the PK of first- and second-line TB drugs with and without antiretrovirals in pregnant women, has enrolled 10 women. An abstract with interim results regarding the PK of isoniazid and rifampin has been accepted for presentation at the International AIDS Society Conference on HIV Science in July.[83]

A recently established cross-network TB and Pregnancy Research Working Group (TBPWG) has fostered collaborations among researchers and networks to enable data sharing between THSEPISO and P1026s to better characterize the PK of first-line TB drugs in pregnant and postpartum women. A population PK model combining PK, safety, and outcomes data from THSEPISO and P1026s is planned and will be proposed to the IMPAACT network in 2017. The TBPWG has also submitted a concept sheet to the TBTC's Core Science Group proposing an observational study of TB treatment in pregnant and postpartum women who screen out of TBTC S31/ACTG 5349—a phase III study evaluating whether rifapentine-containing regimens can shorten treatment for DS-TB (see TB Treatment Pipeline, in *2017 Pipeline Report*, [publishing July 2017]).

Despite these encouraging advancements and collaborative efforts, there is still an urgent need to support the earlier inclusion of pregnant women in TB drug trials.[84,85]

Recommendations

Pediatric TB treatment R&D has come a long way in recent years. Studies to fill longstanding PK and safety data gaps are producing results, and those to evaluate shortened and simplified prevention and treatment regimens are already underway or are soon to open. Yet much work remains to simplify and improve the treatment of DR-TB in children and to bring pediatric formulations of new and second-line TB drugs to market.

For researchers

- Determine whether exposures achieved using recommended doses of first-line drugs in children result in good outcomes, even if they do not match the levels of exposure achieved in adults. This evidence is crucial in the context of shortened regimens and for treatment of the wide spectrum of TB disease seen in children.

- Include children with TB in pediatric studies of new antiretrovirals and children with HIV in pediatric TB studies. PK substudies in TB/HIV-coinfected children are needed to evaluate safety and DDIs to inform appropriate dosing.
- Determine optimal regimens and doses to improve outcomes in children treated for TBM, which have remained abysmal and unchanged for the past 50 years.[86]

For drug and study sponsors

- Expedite the investigation of new drugs and regimens in children. Pediatric investigation of new TB drugs and regimens should begin as soon as indications of efficacy and safety have been established in adults (phase IIb studies); cohorts for PK and safety studies in children should be recruited in parallel. Adolescents aged 10 years and older should be included in adult TB drug trials phase IIb and later as a matter of urgency.[87]

For regulatory authorities

- Ensure the timely and comprehensive collection and submission of pediatric data to inform the safe and appropriate use of new TB drugs in children.

For policy makers

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children. Given the amount of data on the PK of second-line TB drugs that have emerged since 2006 (the first and last time the WHO recommended doses for second-line TB drugs in children), the WHO should immediately take steps necessary to issue updated dosing guidelines for second-line TB drugs in children.

For donors

- Increase investments in pediatric TB drug R&D to support the progressively full roster of studies necessary to improve the treatment of all forms of TB in children. Global investments in pediatric TB drug R&D totaled just $16.1 million in 2015.[88]
- Unitaid, whose investments led to the market introduction of appropriately dosed pediatric FDCs of first-line TB drugs, should fund a similar project to expedite development and market introduction of pediatric second-line TB drugs. Pediatric DR-TB is a small and fragile market, for which medicines vital to catalyzing better treatment of DR-TB in children are highly unlikely to be developed without external incentives.

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